5183a ↓

Special Communication

Report to the Secretary of HEW From the Medical Advisory Group on Cyclamates

Roger O. Egeberg, MD; Jesse L. Steinfeld, MD; Ivan Frantz, MD; George C. Griffith, MD; Harvey Knowles, Jr., MD; Edward Rosenow, MD; Henry Sebrell, MD; and Theodore Van Itallie, MD

The Medical Advisory Group on Cyclamates appointed by Secretary Finch met on Nov 17 and 18, 1969, with representatives of the Food and Drug Administration and the National Institutes of Health to review the currently available data on the possible harmful effects of these nonnutritive sweeteners in relation to their potential benefits. The group considered the data on carcinogenic, mutagenic, teratogenic, enzymatic, osmotic, and growth effects of cyclamates and on their possible adverse influence in interaction with other drugs.

For editorial comment see page 1367.

After carefully reviewing the evidence currently available, the Medical Advisory Group on Cyclamates unanimously supported the secretary's prohibition of the inclusion of cyclamates in beverages for general use, and in the future processing of general purpose foods and vegetables. It recognized, however, that in the medical management of individuals with diabetes (and particularly in the case of juvenile diabetes) or patients in whom weight reduction and control are essential for health, nonnutritive sweeteners such as cyclamates can be a useful dietary adjunct. The advisory group was of the opinion that the medical benefits in these instances outweighed the possibility for harm and recommended that cyclamates and products containing cyclamates continue to be made available to such patients on a nonprescription drug-labeled basis and should be used only on the advice of a physician.

The advisory group recommended further (1) that products containing cyclamates display a cautionary label that includes the cyclamate content in an average serving; (2) that cyclamates no longer be used as an excipient (sweetener or inactive ingredient in drug manufacture); (3) that research be continued on cyclamates and other nonnutritive sweeteners to reproduce and expand the present findings; and (4) that FDA annually carry out a review of data on cyclamates and other nonnutritive sweeteners to determine whether research developments require a revision or addition to these recommendations.

Background

The substitution of nonnutritive sweetening agents for sugar began with the discovery of saccharin in 1879 (sweetening power 350 times sugar) and was greatly extended when the sweetening properties of cyclamates (sweetening power 30 times sugar) were noted in 1944. Combinations of cyclamates and saccharin (30 to 100 times as sweet as sugar) avoid the objectionable aftertaste of saccharin but take advantage of its sweetening properties. In 1968, 17 million lb of cyclamates were manufactured: 69% were used in beverages, 19% in table sweeteners, 6% in foods, 4% in nonfood items, and 2% were exported.

From the Department of Health, Education, and Welfare (Dr. Egeberg [*Chairman*]), and Office of the Surgeon General, Public Health Service (Dr. Steinfeld), Washington, DC; University of Minnesota, Minneapolis (Dr. Frantz); School of Medicine, University of Southern California, Los Angeles (Dr. Griffith); University of Cincinnati, Cincinnati, Ohio (Dr. Knowles); American College of Physicians, Philadelphia (Dr. Rosenow); and Columbia University (Dr. Sebrell), and St. Lukes Hospital (Dr. Van Itallie), New York.

Reprint requests to Surgeon General of the Public Health Service, Department of Health, Education, and Welfare, Washington, DC 20201 (Dr. Steinfeld).

The Food Additives Amendment (1958) to the Federal Food, Drug, and Cosmetic Act (1938) specifically exempted from the law substances generally regarded as safe (GRAS) but authorized the Food and Drug Administration to alter or ban the use of such substances on the basis of safety evaluation.

The negative findings on toxicity in earlier FDA studies (1951), other than stool softening and diarrhea in rats, and the finding (1955)[1] by the National Academy of Sciences-National Research Council (NAS-NRC) Food Protection Committee of no nutritional or public health problem from regulated use of cyclamates in *special purpose foods*, prompted the inclusion of cyclamates and saccharin in the 1959 GRAS list.

At this time, cyclamates were not used so extensively nor in such a wide array of foods as today. Although the NAS-NRC committee report concluded that a maximum intake of 5 gm daily would be acceptable, a "no limit" recommendation was accepted, as the sweetener was used primarily in tablets which contained only 0.05 gm of cyclamate so that more than 100 tablets a day would have to be taken to exceed the 5 gm maximum intake. However, the increased number of people using cyclamate sweetened food in an attempt to control weight greatly increased cyclamate consumption. In response, the NAS-NRC committee in 1962 issued a revised policy statement saying that cyclamates could safely be used in limited amounts as a nonnutritive substitute for sugar in special purpose foods. In both 1965 and 1967, scientists of FDA evaluated available information on cyclamates and concluded that there was no evidence that use levels at that time presented a hazard to health. In 1967, the joint Food and Agriculture Organization-World Health Organization FAO-WHO Expert Committee on Food Additives[2] established an unconditional acceptable daily intake of 0 to 5 mg/kg of body weight for saccharin, and a temporary acceptable daily intake of 0 to 50 mg/kg for cyclamates until additional studies, including those on the toxicity of cyclohexylamine, could be carried out within the next three years.

The NAS-NRC in 1968 evaluated all available data, including the FAO-WHO report, and recommended an acceptable daily intake of 70 mg/kg of body weight for cyclamates. Total daily doses of 1 gm of saccharin or 5 gm or less of cyclamate were considered safe. In this same year, the FDA proposed a maximum limit of 3.5 gm of cyclamate for a 70 kg (154 lb adult and 1.2 gm for a 25 kg (54 lb) child. In the following year, FDA proposed that labeling be modified to permit the consumer to determine easily if his intake was below recommended limits.

Evidence of Possible Hazard

Beginning in 1967 and extending to the present, a number of research findings have raised questions as to the safety of the cyclamates. The discovery of bladder tumors in animals is directly responsible for the removal of cyclamates from the list of substances generally recognized as safe for use in foods. On June 5, 1969, scientists at the University of Wisconsin reported to Abbott Laboratories, who were supporting the studies, that a significant incidence of bladder tumors had been found in white Swiss mice in two experiments in which pellets of cholesterol and cyclamates were implanted into the lumen of the urinary bladder. Representatives of Abbott Laboratories carried out discussions with representatives of the National Cancer Institute and the Food and Drug Administration, and all concerned agreed that carcinogenicity demonstrated by the pellet implantation technique did not provide relevant information as to the hazards of orally ingested compounds, a position which had previously been taken by an NAS-NRC Ad Hoc Committee on Non-Nutritive Sweeteners in 1968. However, these studies did stimulate new experiments and encouraged scientists conducting studies then in progress to give special attention to the bladder as a site of neoplastic transformation.

On Oct 8, 1969, an Abbott scientist was notified that there appeared to be bladder lesions in rats fed a 10:1 mixture of cyclamate sodium: saccharin sodium over a two-year period in their contract-supported experiments at the Food and Drug Research Laboratories, Long Island, NY. During this study, many of these rats were shown to be able to convert cyclamate to cyclohexylamine (CHA). In the 79th week, half of the animals in each treated group were given supplemental CHA in the diet.

On Oct 9, pathologists of Abbott Laboratories examined slides from an experiment initiated by Abbott in 1967 and conducted at Industrial Bio-Test Laboratories, Inc., Northbrook, Ill. In these experiments cyclohexylamine (CHA), a known impurity of commercial cyclamate and a metabolic breakdown product of cyclamate, was fed to rats at various levels over a period of two years. One tumor was found in the bladder of one of the 17 surviving rats on the highest daily dosage of 15.0 mg/kg of CHA.

On Oct 13, representative of Abbott Laboratories met with scientific personnel of the Food and Drug Research Laboratories to review the study of cyclamate sodium and saccharin sodium. Of the 240 rats receiving the cyclamate sodium: saccharin sodium mixture, seven males and one fe-

male showed papillary lesions of the urinary bladder, a tumor rarely observed in rats. However, the tumors were seen macroscopically in only two animals. All lesions occurred in the group of 35 males and 45 females fed 2.5 gm/kg/day of the cyclamate sodium: saccharin sodium mixture, and none were found at 1.00 gm/kg/day or below. Of the eight tumors, four to eight were diagnosed as carcinomas by different pathologists. Three of the animals with bladder tumors had received supplemental CHA and five had not. With one exception, tumors developed in rats found to convert cyclamate to CHA.

On Oct 14 representatives of Abbott Laboratories, National Cancer Institute, FDA, and the Department of Health, Education, and Welfare met to discuss these preliminary findings, and it was agreed that the scientific personnel present would report the findings to the NAS-NRC Ad Hoc Committee on Non-Nutritive Sweeteners the morning of Oct 17. At this time the committee recommended cyclamates be removed from the GRAS list.

On Oct 18, 1969, HEW Secretary Robert H. Finch, because of the demonstration of urinary bladder tumors in rats fed cyclamate throughout their life span, ordered the artificial sweetener cyclamate removed from the GRAS list. This action was taken in accordance with the Delaney Amendment and on the advice of medical consultants to the secretary. The secretary emphasized in the strongest possible terms that there was no evidence that cyclamate causes cancer in humans. Further, there was no evidence that the use of cyclamates had caused malformation in children or any other abnormality in humans, other than a rare skin hypersensitivity.[3-5]

Since the Oct 18 announcement by the secretary, additional evidence has come to light. In an FDA feeding study, originally designed to determine the conversion of cyclamate to cyclohexylamine, infiltrating bladder tumors were found at 88 weeks in three of 23 rats of the Osborne Mendel strain. The rats had been fed cyclamate without saccharin at daily rates as low as 400 mg/kg of body weight. This is about one-sixth the dosage fed to the different strain of rats used in the Abbott study. No tumors were found in the control groups. Bladder tumors were found by the FDA study in two rats, one male and one female, even in those animals receiving 400 mg/kg daily. The minimum dosage used. At this time, therefore, the lowest dosage of cyclamate capable of producing bladder carcinoma in rats is not known.

Although the action taken by the secretary of HEW in regard to cyclamates was based solely on the finding of carcinogenicity in animals, consideration of other research findings also is important. In these studies, toxicity of cyclohexylamine (CHA), as well as cyclamates, must be considered since most species fed cyclamates develop the capacity to convert cyclamates to CHA and most foods containing cyclamates also contain small quantities of CHA. Humans capable of converting cyclamates to CHA will metabolize 0.1% to 38% of the ingested cyclamate to CHA.[6] Cyclohexylamine has a 50% lethal dose (LD_{50}) in rats of 200 mg/kg and in humans[7] will cause dermatitis and convulsions at high doses.

It has been reported[8] that the addition of cyclamate (200μg/ml) to leukocyte cultures produced chromosome breaks. Using kidney cells from a marsupial (rat kangaroo) Sidney Green, MS, et al (unpublished data) found that similar concentrations of cyclamate did not inhibit mitosis or produce chromosome abnormalities, but cyclohexylamine at concentrations as low as 1μg/ml produced single chromatid breaks. In vivo experiments in rats[9] showed that cyclohexylamine, 1 mg/kg, injected daily for five days produced a significant increase in single chromatid breaks (discontinuity of the chromatin of at least the width of its chromosome) in spermatogonial cells and that injected doses of 10 mg/kg of cyclohexylamine for five days showed a significant increase in chromatid breaks in bone marrow cells.

Injection of various compounds including cyclamates, CHA, sucrose, and alcoholic solvents into the air sacs of eggs have shown that cyclamates cause almost six times as many, and CHA causes 60 times as many deformities of the embryo as sucrose.[10]

The significance of these experiments and what relevance, if any, they have to man cannot be evaluated with present knowledge.

Medical Effects of Cyclamates and Cyclohexylamine

Cyclamates produce stool softening and diarrhea in humans when relatively large amounts are ingested. This is apparently the result of an osmotic effect; there is no evidence that cyclamates exacerbate organic gastrointestinal diseases. A number of cases of photosensitivity have also been reported in users of artificially sweetened products.

Various pharmacologic effects of cyclamates and cyclohexylamine may influence the action of certain commonly used drugs and thus interfere with therapeutic regimens. Cyclohexylamine produces weak pressor effects when administered to animals, raising the possibility that hypertensive reactions might result in humans, particularly those being treated with monoamine oxidase inhibitors. In rats, pretreatment with cyclamate (100 mg/kg

body weight subcutaneously) reduces the hypoglycemic effect of tolbutamide, but similar pretreatment increases the hypoglycemic effect of chlorpropamide.[11] Cyclamates may potentiate the diuretic effects of the thiazide drugs and excess loss of potassium may occur. Studies in some animal species indicate that cyclamates potentiate the anticoagulant effect of the coumarin drugs suggesting that exaggerated responses in patients under anticoagulation regimens may occur.[12] Cyclamates bind moderately strongly to plasma protein and may displace other drugs similarly bound with resultant modifications in pharmacologic effect. Other studies have shown that the absorption of the antibiotic lincomycin is reduced by cyclamates; there is no evidence suggesting effects on the absorption of other similar drugs.[13]

Presently available data suggest that special care should be taken when cyclamates are used in patients under treatment with other drugs. Because of the paucity of reported clinical experience with cyclamates, instances of known or suspected adverse effects of the cyclamates as outlined above should be reported promptly to the Director, Bureau of Medicine, Food and Drug Administration, Washington, DC 20024.

Medical Uses of Cyclamates

Although the use of cyclamates is not absolutely necessary in any disease, it can be useful in the medical management of individuals with diabetes of patients in whom weight reduction and control is essential to health. Particularly in juvenile patients who have diabetes, where sweets and soft drinks are a special problem, nonnutritive sweetened foods may be an essential part of preventive therapy.

Excessive glucosuria may cause symptomatic polyuria, moniliasis, and pruritus with bacterial infection of the urologic system leading to pyelonephritis. Hyperglycemia is thought by some to be related to angiopathy, neuropathy, cataracts, and pregnancy abnormalities. Although it is not known for sure whether obesity adds to the risk of angiopathy in the patient with established diabetes, certainly all agree that obesity is an undesirable physical state whether diabetes is present or not. Therefore, a sugar substitute can be helpful in the dietary management of the young diabetic and the overweight patient.

As cyclamates are withdrawn, care must be taken by physicians that diabetic or obese patients carefully note the sugar content of diet drinks since these drinks may be sweetened with combinations of saccharin and sugar. It is emphasized that cyclamates will continue to be allowed only in special purpose foods. The restriction on cyclamate use in marketed beverages will be absolute, beginning Jan 1, 1970.

In all cases where cyclamates are used in foods, the lowest exposure possible for each individual seems the most reasonable course.

There is no medical justification for cyclamates as an excipient for drug formulation. For the present, cyclamate will be available on a drug labeled, nonprescription basis and should be used only on the advice of a clinician.

Over the last several decades there has been a slow, steady increase in incidence, but not mortality rate, from bladder cancer in the United States. But it should be emphasized that there has been no significant change in this trend during the period that cyclamates have been used as an artificial sweetener.

Further updating of such data will be accumulated and reported as soon as possible.

References

1. *National Academy of Sciences-National Research Council; The Safety of Artificial Sweeteners for Use in Foods*, publication 384, 1955.

2. *Specifications for the Identity and Purity of Food Additives and Their Toxicological Evaluation; Some Flavoring Substances and Non-nutritive Sweetening Agents*, 11th report, publication 44. Rome, Food and Agriculture Organization and World Health Organization Expert Committee on Food Additives, 1968.

3. Boros E: An experience with artificial sweeteners. *JAMA* 194:571-572, 1965.

4. Kobori, R, Araki H: Photoallergy. *J Asthma Res* 3:213-215, 1966.

5. Lamberg SI: A new photosensitizer: The artificial sweetener cyclamate. *JAMA* 201:747-750, 1967.

6. Coulston FV, Golberg L: *FDA Progress Report on Contract 69-7*. Albany Medical College, Union University, Institute of Experimental Pathology and Toxicology, 1969.

7. Lomonova GV: Toxicity of cyclohexylamine and dicyclohexylamine. *Gig Tr Prof Zabol* 7:95-98, 1961.

8. Stone D, Lamson E, Chang YS, et al: Cytogenetic effects of cyclamates on human cells in vitro. *Science* 164:568-569, 1969.

9. Legator MS, Palmer KA, Green S, et al: Cytogenetic studies in rats of cyclohexylamine, a metabolite of cyclamate. *Science* 165:1139-1140, 1969.

10. Verret MJ: *Teratogenic Effects of Cyclamate and Related Compounds in the Chicken Embryo: Report on Non-nutritive Sweeteners*. Bureau of Science-Bureau of Medicine, Food and Drug Administration, III-24, 1969.

11. Lockwood RR; Dixon, RL: The effect of cyclamate on the hypoglycemic response of tolbutamide and chlorpropamide in rats. *Food Cosmet Toxic* 7:1-7, 1969.

12. Holcenberg JS; Bidgood M; Dixon, RL: Possible interaction between cyclamate and warfarin. *Curr Ther Res* 11:577-584, 1969.

13. Wagner JJ: The bitter sweeteners. *Sciences* 9:20-25, 1969.